Atomoxetine Treatment for Pediatric Patients with ADHD and Comorbid Anxiety

Calvin Sumner, MD[1]; Lawrence Sher, MD[2]; Virginia Sutton, PhD[1]; Rosalie Bakken, PhD[1]; Martin Paczkowski, MPH[1]; Douglas Kelsey, MD, PhD[1]

[1]Lilly Research Laboratories, Indianapolis, IN; [2]Peninsula Research Associates, Inc. Rolling Hills Estates, CA

ABSTRACT

Background: Research indicates 25-50% comorbidity of anxiety disorders with attention-deficit/hyperactivity disorder (ADHD). Atomoxetine is a nonstimulant approved for treating ADHD that is not contraindicated in the presence of anxiety disorders.

Objective: This study compared atomoxetine to placebo in treating pediatric patients with ADHD and comorbid anxiety, as measured by the ADHDRS-IV-Parent:Inv (ADHD RS) Total Score and the Pediatric Anxiety Rating Scale (PARS) total Score.

Methods: Patients in this double-blind, acute portion of an extended, multicenter trial were randomized to approximately 12 weeks of atomoxetine treatment (n=87) or placebo (n=89). Patients met DSM-IV criteria for both ADHD and anxiety disorder (generalized anxiety, separation anxiety, or social phobia). ADHD RS and PARS total scores were analyzed using ANCOVA (LOCF). Patients who responded during a placebo lead-in period were excluded from ADHD RS and PARS (total scores) analyses.

Results: Mean ADHD RS Total score improved significantly from baseline to endpoint for the atomoxetine group (n=55; -10.5, SD 10.6) relative to placebo (n=58; -1.4, SD 8.3; $p<.001$). Mean PARS total score also improved significantly from baseline to endpoint for the atomoxetine group (n=55; -5.5, SD 4.8) relative to placebo (n=58; -3.2, SD 5.0; $p=.011$).

Conclusion: Results suggest atomoxetine is efficacious and well tolerated in pediatric patients with ADHD and comorbid anxiety.

BACKGROUND

Attention-deficit/hyperactivity disorder (ADHD)

- Affects 3% to 7% of school-aged children in the United States (APA, 2000).
- Characterized by inattention and/or hyperactivity and impulsivity

ADHD and Comorbid Anxiety

- Recent research indicates a 25% to 50% comorbidity of anxiety disorders with ADHD (Bird et al., 1993; Biederman et al., 1991)

Atomoxetine

- Atomoxetine is a potent inhibitor of the presynaptic norepinephrine transporter and is the first non-stimulant approved for ADHD treatment in children, adolescents, and adults.
- The efficacy of atomoxetine for treating ADHD has been demonstrated in children and adolescents when administered once daily (Kelsey et al., 2004; Michelson et al., 2002) or twice daily (Michelson et al., 2001; Spencer et al., 2002).
- The efficacy of atomoxetine in pediatric patients with ADHD and comorbid anxiety is not known.

OBJECTIVE

This study compared atomoxetine to placebo in treating pediatric patients (children and adolescents) with ADHD and comorbid anxiety.

METHODS

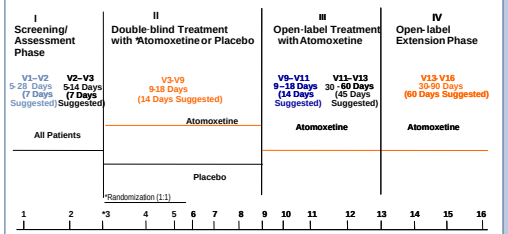
Patients

- Children and adolescents, 8-17 years of age
- Met DSM-IV criteria for both ADHD and anxiety disorder (generalized anxiety, separation anxiety, or social phobia)
- Had an ADHD symptom severity score at least 1.5 standard deviations above age and gender norms as assessed by the ADHD Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHD RS) (DuPaul et al., 1998; Faries et al., 2001) for the total score or either of the inattentive or the hyperactive/impulsive subscales

Study Design

- Randomized, double-blind, placebo controlled, multicenter trial
- Patients randomized to approximately 12 weeks of atomoxetine or placebo
- The target atomoxetine dose (1.2 mg/kg/day) could be increased to 1.8 mg/kg/day for patients not responding adequately
- All daily doses were split and administered BID

Study Design



*For subjects randomized to atomoxetine, the site personnel and subjects were blind to the timing and duration of placebo treatment. Only data from periods I and II are presented here.

Primary Efficacy Measures

- ADHD-RS (18 items corresponding to the DSM-IV diagnostic symptoms of ADHD)
- Pediatric Anxiety Rating Scale (PARS; an interview-based scale used to rate the severity of anxiety symptoms)

Secondary Efficacy Measure

- Multidimensional Anxiety Scale for Children (MASC)

Statistical Analyses

- ADHD RS and PARS total scores were analyzed using analysis of covariance (last observation carried forward)
- Fisher's exact test was used for categorical analyses
- The statistical analysis plan pre-specified that patients who responded during a placebo lead-in period would be excluded from the co-primary analyses (ADHD RS and PARS)

RESULTS

Patient Demographics

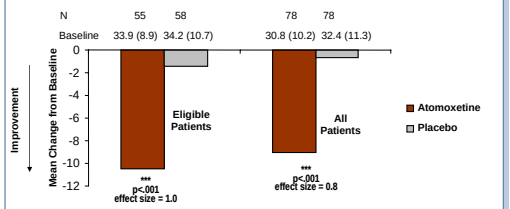
		Atomoxetine (n=87)	Placebo (n=89)
Age	Mean (std)	12.2 (2.8)	11.8 (2.5)
Origin		79.3%	82.0%
Gender			
	Male	62.1%	67.4%
	Female	37.9%	32.6%
Subtype			
	Combined	75.9%	74.2%
	Inattentive	23.0%	24.7%
	Hyp/Impulsive	1.2%	1.1%
Prior Stimulant	YES	60.9%	64.0%
Exposure	NO	39.1%	36.0%
CYP2D6	EM	95.4%	89.5%
Genotype	PM	4.7%	10.5%
Height in cm	Mean (std)	150.2 (16.2)	150.1 (14.2)
Weight in kg	Mean (std)	47.8 (16.7)	45.8 (15.1)

Patient Disposition

	Atomoxetine (N=87)	Placebo (N=89)	Fisher's p value
Complete SP II	66 (76%)	66 (74%)	.862
Adverse Event	2 (2%)	1 (1%)	.619
Lack of Efficacy	10 (11%) †	13 (15%)	.656
Lost to Follow-Up	2 (2%)	1 (1%)	.619
Protocol Violation	2 (2%)	4 (5%)	.682
Patient Decision	4 (5%)	4 (5%)	1.00
Sponsor Decision	1 (1%)	0 (0%)	.494

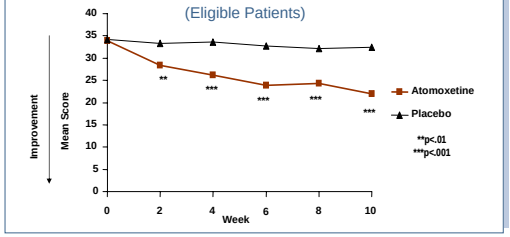
† 6 of the atomoxetine patients discontinued due to lack of efficacy during the placebo lead-in

ADHD RS Total Score

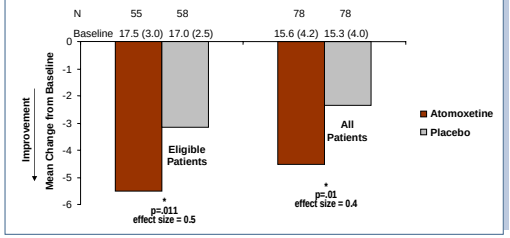


ADHD RS Total Score-MMRM

(Eligible Patients)

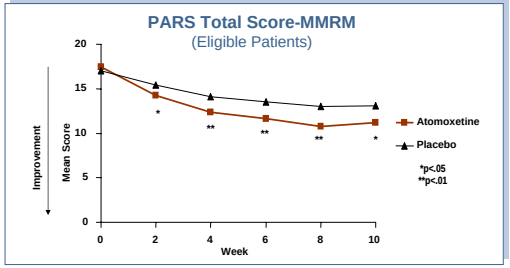


PARS Total Score

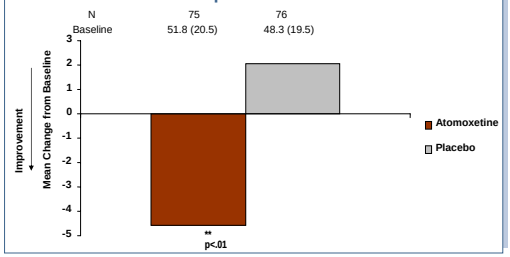


PARS Total Score-MMRM

(Eligible Patients)



MASC Imputed Total Score



Exposure and Total Daily Dose (mg/kg/day)

All Randomized Patients Who Took at Least One Dose of Study Drug

Mean (SD)	Atomoxetine (N=77)	Placebo (N=80)
Days of Therapy	78 (16)	73 (19)
Final Dose	1.3 (0.3)	N/A
Modal Dose	1.2 (0.3)	N/A
Maximum Dose	1.3 (0.3)	N/A

Treatment-Emergent Adverse Events (Incidence ≥ 5%)

All Randomized Patients Who Took at Least One Dose of Study Drug

	Atomoxetine (N=77)	Placebo (N=80)	Fisher's p value
Decreased Appetite	11 (14.3%)	3 (3.8%)	.025
Headache	11 (14.3%)	7 (8.8%)	.323
Abdominal Pain Upper	9 (11.7%)	4 (5.0%)	.155
Vomiting	8 (10.4%)	4 (5.0%)	.241
Irritability	5 (6.5%)	3 (3.8%)	.490
Nasopharyngitis	5 (6.5%)	5 (6.3%)	1.00
Nausea	5 (6.5%)	2 (2.5%)	.270
Cough	4 (5.2%)	5 (6.3%)	1.00
Influenza	4 (5.2%)	1 (1.3%)	.204
Sinusitis	4 (5.2%)	3 (3.8%)	.716

CONCLUSIONS

- Atomoxetine demonstrated significant efficacy in patients with ADHD and comorbid anxiety
- Atomoxetine demonstrated a large effect size (1.0) in ADHD (ADHD RS) and a moderate effect size (.5) in anxiety (PARS)
- Patients reported improvements in anxiety consistent with investigator ratings (MASC)
- The primary results were positive in all patients as well as eligible patients (those who did not respond during the placebo lead-in)
- Atomoxetine was well tolerated in patients with ADHD and comorbid anxiety

References

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR.* Washington, DC: American Psychiatric Association; 2000.

Biederman J, Newcorn J, Sprich S. Comorbidity of attention-deficit/hyperactivity disorder with conduct, depressive, anxiety and other disorders. Am J Psych 1991;148:564-577.

Bird H, Gould M. Staghezza B. Patterns of diagnostic morbidity in a community sample of children aged 9 through 16 years. J Am Acad Child Adolesc Psychiatry 1993;32:361-368.

DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD rating scale-IV: checklists, norms, and clinical interpretations. New York, The Guilford Press, 1998

Faries DE, Yalcin I, Harder D, Heiligenstein JH. Validation of the ADHD Rating Scale as a Clinician Administered and Scored Instrument. Journal of Attention Disorders 2001;5:39-47.

Kelsey DK, Sumner CR, Casat CD, Coury DL, Quintana H, Saylor KE, Sutton VK, Gonzales J, Malcolm SK, Schuh KJ, Allen AJ. Once-daily atomoxetine treatment for children with attention-deficit/hyperactivity disorder, including an assessment of evening and morning behavior: a double-blind, placebo-controlled trial. *Pediatrics* 2004;114(1):e1.

Michelson D, Allen J, Busner J, Casat C, Dunn D, Kratochvil C, et al. D. Once-daily atomoxetine treatment for children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled study. Am J Psychiatry 2002;159:1896-1901.

Michelson D, Faries DE, Wernicke J, Kelsey D, Kendrick K, Sallee FR, et al. Atomoxetine in the treatment of children and adolescents with ADHD: A randomized, placebo-controlled dose-response study. Pediatrics 2001;108:e83.

Spencer T, Heiligenstein, JH, Biederman J, Faries DE, Kratochvil CJ, Conners CK, Potter WZ. Results from 2 proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 2002;63(12):1140-1147.

Funding provided by Eli Lilly and Company